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A SEMI-EMPIRICAL AND AB-INITIO ANALYSIS OF FLUOROKETONES AS REACTIVE ELECTROPHILES

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SUMMARY

Fluoroketones have long been known as highly reactive, electrophilic carbonyl compounds and have become increasingly important as inhibitors of hydrolytic enzymes. The enhanced electrophilicity of fluoroketones relative to ketones has been presumed to be due to carbonyl polarization. Results of MNDO and 6-31G** calculations presented in this study argue against this explanation and provide a rationale based on the relative energy of the acceptor (LUMO) orbitals for fluoroketones and ketones. Fluoroketones acceptor orbital energy levels were found to be 21.2 to 28.4 kcal/mole lower than the analogous ketone.

INTRODUCTION

Fluoroketones have long been known as highly reactive, electrophilic carbonyl compounds which are readily susceptible to nucleophilic attack. Indeed, fluoroketones exist predominantly as the hydrate in aqueous solution [1]. This tendency to form stable, tetrahedral species has led to the development of highly potent and specific inhibitors for a wide variety of esterase enzymes [2]. Mechanistic studies of enzyme inhibition indicate that nucleophilic addition of the active site serine residue to the fluoroketone carbonyl results in a tightly bound hemi ketal which resembles the transition state for enzyme catalyzed ester hydrolysis [3]. Although comprehensive studies on the thermodynamics of keto/hydrate equilibria of fluoroketones have appeared [1], no kinetic rationale for the enhanced electrophilicity of

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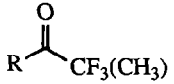
fluoroketones relative to structurally analogous ketones has been provided. The enhanced electrophilicity has been presumed to be due to carbonyl polarization or a substantial positive electrostatic point charge on the fluorocarbonyl carbon. In this paper, we report that neither carbonyl polarization nor electrostatic point charge considerations can account for the enhanced relative reactivity towards nucleophilic addition of fluoroketones compared to ketones [4].

Computational studies of fluorinated molecules pose several problems. Development of MNDO [5] provided considerable improvement over MINDO/3 [6]; yet, MNDO still retained some deficiencies, such as over estimation of F-F repulsions, leading to errors for highly fluorinated compounds. Nevertheless, in the cases studied by Dewar and Rzepa [5c], MNDO predicted geometries agreed quite well with experimental observations. Recently Cooper and co-workers [7] have compared several semi-empirical and ab-initio calculation methods for fluorocarbons. The conclusion from these studies indicated that MNDO calculated C-F bond distances were in reasonable agreement with experimental data; however, the best results were obtained using the 6-31G basis set with polarization functions on fluorine. The studies of Cooper et al. concluded that ab-initio SCF calculations with relatively small basis sets (STO-3G) can give accurate geometries and realistic Mulliken charges. In this regard, results from MNDO and STO-3G calculations were very comparable [7b].

In an effort to analyze the relative reactivity of fluoroketones, a series of model compounds **1-8** were chosen based on the extensive list of structures examined as enzyme inhibitors.



1	$R = CH_3CH_2$-	**5**	$(CH_3)_2{=}CH$-
2	$HC{\equiv}C$-	**6**	H_2NCH_2-
3	$CH_3C{\equiv}C$-	**7**	(S)-$CH_3CH(NH_2)$-
4	$CH_2{=}CH$-	**8**	CH_3SCH_2-

Electrostatic point charges, carbonyl polarization, and the acceptor level energy were determined by MNDO SCF-MO calculations. The data obtained would provide a basis for the direct comparison of trifluoromethyl and methyl ketones. The choice of MNDO seemed realistic given the arguments presented above [5-7] as well as the fact that the compounds under consideration were not highly fluorinated. For the sake of comparison, ab-initio calculations using the 6-31G** basis set [8] were also carried out.

EXPERIMENTAL

Computational Methods

Geometry optimization was initially carried out by molecular mechanics calculations using the entire set of potential functions with a block diagonal Newton-Raphson minimization procedure. The geometries for each model compound were then fully optimized by MNDO SCF-MO calculations (MOPAC version 3.10 obtained from QCPE run on a Microvax II or MOPAC version 5.10 run on a Tektronix CAChe® molecular modeling workstation). This procedure provided the input parameters for the ab-initio Hartree-Fock calculation at the 6-31G** level (Cray 2 version of Gaussian 86 [9]).

Spectral Data

Decoupled (C-H) ^{13}C NMR data were obtained on a GN-300 spectrometer in deuterochloroform. The chemical shifts are reported relative to tetramethylsilane. Trifluoroacetone and trifluoroacetophenone were obtained from Aldrich. 1, 1, 1-Trifluoropentan-2-one [10], 1, 1, 1-trifluoro-3-octyn-2-one [11] and 3-octylthio-1, 1, 1-trifluoropropan-2-one [2c] were prepared by literature procedures. 1, 1, 1-Trifluoro-3-octen-2-one was prepared by lithium aluminum hydride reduction of the acetylenic ketone (4 eq. refluxing THF) followed by oxidation [12] of the carbinol. 1-Octylthiopropan-2-one was prepared from bromoacetone [2c].

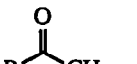
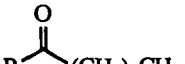
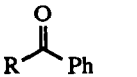
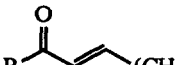
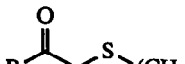
RESULTS AND DISCUSSION

An indication that the reactivity of fluoroketones compared to ketones could not be explained by the electrophilicity of the carbonyl carbon can be obtained from an analysis of ^{13}C NMR data. The chemical shift provides a measure of the electron density at carbon. In general, more positive character is reflected by a downfield shift. Inductive effects (among others such as anisotropy or diamagnetic shielding) of an electronegative substituent clearly reveal significant downfield shifts relative to hydrogen[13]. The trifluoromethyl group is regarded as a strong electron withdrawing substituent [14] and would be expected to cause a downfield shift for the carbonyl carbon relative to the structurally analogous methyl ketone. However, upon examination of ^{13}C NMR data for several CF_3/CH_3 ketone pairs, Table 1, the opposite trend is revealed. For example, acetone CO is observed at 206.0 ppm while trifluoroacetone CO appears 17.2 ppm upfield at 188.8 ppm. For the six compounds examined, the fluoroketone CO carbon appeared 16.3 to 18.7 ppm upfield from the corresponding methyl ketone CO carbon.

The MNDO calculation results for heat of formation; electrostatic point charges, and the derived carbonyl polarization are given in Table 2. Although the partial charge at carbon is actually slightly larger for the fluoroketone model compounds, the charge difference (no greater than 0.02 e) does not seem to adequately explain the considerable difference in reactivity. As an illustrative point, aldehydes are more reactive than ketones toward hydration. Acetaldehyde exhibits a $t_{1/2}$ for hydration of only 1 min (H_2O, 25°C) [15]. Trifluoroacetophenone is even much more reactive than acetaldehyde, $t_{1/2}$ for hydration equals 0.22 sec (10:1, H_2O: CH_3CN, 23°C). [16] When carbonyl polarization for compounds **1-8** is compared (Table 2), polarization is actually greater for each of the methyl ketones relative to the fluoroketones. Although the reduced carbonyl polarization observed for the fluoroketones can be partially rationalized by charge withdrawal from oxygen to fluorine, the relative polarization seems contradictory to the relative reactivity.

TABLE 1

^{13}C NMR Chemical Shift Data Comparing Trifluoromethyl and Methyl Ketones

Structure	R =	Chemical Shift, CO (ppm) [a]	Δδ(ppm) [b]
	CH_3	206.0 (s)	
	CF_3	188.8 (q, J_{CF} = 36 Hz	-17.2
	CH_3	207.8 (s) [c]	
	CF_3	191.5 (q, J_{CF} = 34 Hz)	-16.3
	CH_3	197.6 (s)	
	CF_3	180.4 (q, J_{CF} = 34 Hz)	-17.2
	CH_3	198.3 (s) [c]	
	CF_3	179.8 (q, J_{CF} = 34 Hz)	-18.5
	CH_3	184.6 (s) [d]	
	CF_3	167.2 (q, J_{CF} = 41 Hz)	-17.4
	CH_3	203.8 (s)	
	CF_3	185.1 (q, J_{CF} = 34 Hz)	-18.7

[a] $CDCl_3$ solution; [b] Difference in chemical shift between CH_3 and CF_3 carbonyl carbon in ppm; [c] **Carbon-13 NMR Spectral Data**, W. Bremser, L. Ernst, B. Franke, R. Gerhards, A. Hardt, and P. E. Lewis, VCH Verlagsgellschaft mbH, D-6940 Weinheim, Germany. 1987; [d] R. J. Linderman, Ph.D. thesis, Univ. Michigan, 1982.

Point charges for the carbonyl carbon and oxygen listed in Table 2 were determined by analysis of Mulliken populations [17]. Mulliken populations derived from ab-initio calculations have been employed by Dixon and co-workers in the study of perfluorocarbanions to assess negative hyperconjugation [18], and in the study of perfluoroenolates to explain β-C

TABLE 2

MNDO calculated values of enthalpy of formation, carbonyl carbon and oxygen electrostatic point charges, carbonyl polarization, acceptor level energy, and the difference between fluoroketone/ketone acceptor level energies.

Model Compound	ΔH_f (kcal/mole)	q_c[a]	q_o[b]	q_c-q_o[c]	LUMO (eV)[d]	Difference[e] eV(kcal/mole)
1-CF_3	-194.28	0.22	-0.21	0.42	-0.55	1.23 (28.4)
1-CH_3	- 53.90	0.21	-0.29	0.49	0.68	
2-CF_3	-127.40	0.35	-0.21	0.56	-0.94	1.08 (25.0)
2-CH_3	- 12.65	0.33	-0.28	0.61	0.15	
3-CF_3	-143.73	0.35	-0.21	0.56	-0.97	1.02 (23.6)
3-CH_3	- 3.69	0.33	-0.28	0.61	0.01	
4-CF_3	-165.16	0.26	-0.23	0.49	-1.02	1.01 (23.3)
4-CH_3	- 24.64	0.25	-0.30	0.55	0.00	
5-CF_3	-177.51	0.27	-0.23	0.50	-1.12	0.92 (21.2)
5-CH_3	- 36.91	0.25	-0.30	0.55	-0.20	
6-CF_3	-182.99	0.17	-0.21	0.38	0.76	1.21 (27.8)
6-CH_3	- 43.52	0.17	-0.29	0.46	0.45	
7-CF_3	-182.35	0.20	-0.21	0.41	0.72	1.23 (28.3)
7-CH_3	- 44.47	0.21	-0.29	0.50	0.51	
8-CF_3	-189.25	0.22	-0.18	0.40	0.64	1.20 (27.6)
8-CH_3	- 49.64	0.22	-0.26	0.48	0.56	

[a]Carbonyl carbon δ^+, [b]Carbonyl oxygen δ^-,[c]Carbonyl polarization, [d]Acceptor level energy,

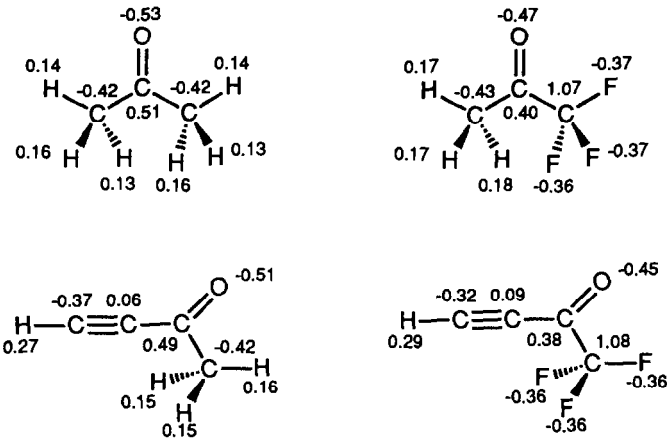
[e]Difference between fluoroketone/ketone acceptor level energies.

electrophilicity [19]. In addition, variations in perfluoroalkane structural parameters have been rationalized by comparing Mulliken populations within a defined set of molecules [7a]. However, there are limitations and potential pitfalls which must be considered when using Mulliken populations [20]. Calculations of SCF wavefunctions with different basis sets may result in the same electron density distribution; however, the corresponding Mulliken population analysis may result in different atomic charges. For this reason, the calculated charges may not be an accurate reflection of the true values; yet, comparison of these data within a defined set of molecules can be employed to rationalize reactivity trends.

Ab-initio calculations at the 6-31G** level were then carried out to lend support to the trend observed in the MNDO calculations. Point charges and carbonyl polarization were calculated (MNDO and 6-31G**) for acetone/trifluoroacetone and 3-butyn-2-one/1, 1, 1-trifluoro-3-butyn-2-one and are given in Table 3. Although the absolute values of the charges determined by MNDO and 6-31G** calculations differed substantially (see figure 1), both the semi-empirical and ab-initio methods exhibited the same general trend. The ab-initio data revealed that the polarization of the fluoroketones relative to that of the methyl ketones is reduced, and more significantly, the partial positive charge of the carbonyl carbon is less for the fluoroketones. Therefore, the ab-initio calculations are apparently in even greater agreement with the experimental evidence than the semi-empirical data. In either event, the calculations and spectral data clearly indicate that partial charge or carbonyl polarization do not account for the observed reactivity patterns.

An alternative explanation was then sought by consideration of a molecular orbital argument. Nucleophilic addition to a carbonyl necessitates the addition of electrons from the HOMO of the nucleophile to the LUMO (the acceptor orbital) of the carbonyl. The acceptor energy is the initial energy of the LUMO level prior to perturbation due to the incoming

6-31 G** point charges :



MNDO point charges :

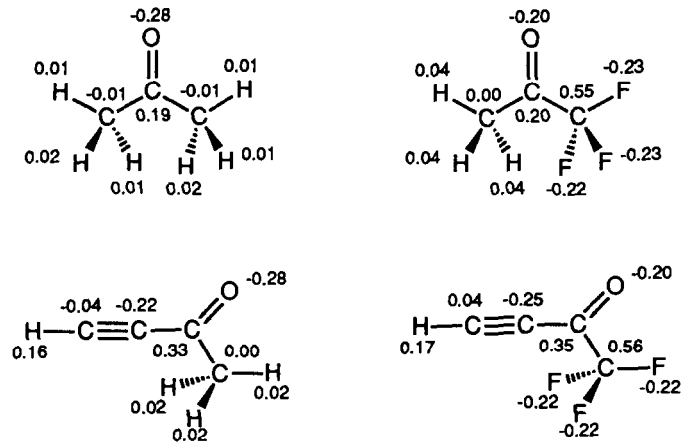


Fig. 1. Comparison of point charges determined by semi-empirical and ab-initio methods for acetone, trifluoroacetone, 3-butyn-2-one and 1,1,1-trifluoro-3-butyn-2-one.

TABLE 3

Comparison of Semi-empirical and Ab-initio Calculations

Calculation method	Structure	R =	q_c[a]	q_o[b]	q_c-q_o[c]	LUMO (eV)[d]	Difference[e] eV(kcal/mole)
MNDO	$RCOCH_3$	CH_3	0.19	-0.28	0.48	0.66	1.28 (29.4)
		CF_3	0.20	-0.20	0.40	-0.62	
6-31G**		CH_3	0.51	-0.53	1.04	4.27	1.42 (32.7)
		CF_3	0.40	-0.47	0.87	2.85	
MNDO	$RCOC{\equiv}CH$	CH_3	0.33	-0.28	0.61	0.15	1.08 (25.0)
		CF_3	0.35	-0.21	0.56	-0.94	
6-31G**		CH_3	0.49	-0.51	1.00	2.59	1.26 (29.0)
		CF_3	0.38	-0.45	0.83	1.33	

[a] Carbonyl carbon δ^+, [b]Carbonyl oxygen δ^-, [c]Carbonyl polarization, [d]Acceptor level energy (π^* or ψ_3), [e]Difference between fluoroketone/ketone acceptor level energies

nucleophile and can therefore provide insight into the energetics of the initial stages of the reaction. The amount of stabilization (ΔE_S) for the HOMO-LUMO interaction is inversely proportional to the initial energy difference of the HOMO and LUMO (ΔE) such that decreasing the LUMO energy or increasing the HOMO energy would serve to decrease ΔE and increase ΔE_S. Stabilization of the acceptor level can be caused by an inductive electron withdrawing effect.

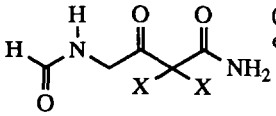
The LUMO energy of each model compound (π^* for the simple carbonyls, ψ_3 for the unsaturated carbonyls) is given in Table 2. The MNDO results show the acceptor level energy of the fluoroketone as consistently lower than that for the analogous methyl ketone. The difference in energy was quite substantial for each trifluoromethylketone/ketone pair, ranging

from 21.2 kcal/mole to 28.4 kcal/mole. A simple aliphatic fluoroketone, **1**-CF_3, provided the greatest stabilization relative to the ketone, **1**-CH_3. The α-heteroatom fluoroketones, **6**-CF_3, **7**-CF_3, **8**-CF_3, each exhibited considerable stabilization, roughly equivalent to the simple aliphatic fluoroketone. The somewhat attenuated stabilizing effect for the unsaturated fluoroketones **2**-CF_3 through **4**-CF_3, is somewhat intriguing given that two electron withdrawing substituents are present on the carbonyl. The stabilization of the LUMO incurred by successive substitution of fluorine for hydrogen was nearly additive at 9.1 kcal/mole, 17.3 kcal/mole, and 28.4 kcal/mole for mono-, di-, and trifluoromethyl substituents, respectively. A somewhat more

$CH_3CH_2COCF_3$	$CH_3CH_2COCF_2H$	$CH_3CH_2COCFH_2$
1.23 eV	0.75 eV	0.40 eV
(28.4 kcal/mole)	(17.3 kcal/mole)	(9.1 kcal/mole)

Acceptor level energy difference from $CH_3CH_2COCH_3$

complex peptidyl fluoroketone [2] was also subjected to the same analytical treatment to provide a calculated acceptor energy level difference of 13.6 kcal/mole between the difluoroketone **9** and the non-fluorinated ketone **10**. Nucleophilic attack is presumed to occur at the ketone CO rather than the amide CO.



0.59 eV (13.6 kcal/mole) acceptor level energy difference from nonfluorinated analog

9 X = F; **10** X = H

The ab-initio calculation results given in Table 3 support the semi-empirical calculations. As observed for the point charges, the ab-initio calculations provided larger acceptor level energy differences (CH_3/CF_3) than the MNDO results. For acetone/trifluoroacetone, the

acceptor level energy difference calculated by MNDO was 29.4 kcal/mole while the ab-initio calculation resulted in an energy difference of 32.7 kcal/mole. Nevertheless, the relative trend for acceptor energy levels by both computational methods parallels that for the point charges and each method is in agreement.

This computational and spectral analysis provides a rationale for the enhanced susceptibility of fluoroketones relative to structurally analogous methyl ketones toward nucleophilic attack. Extrapolation of these data to reflect relative reactivity of the fluoroketones represented in this series may be tenuous and should not be attempted. The calculations can only be viewed toward an understanding of the initial energetics of nucleophilic addition and do not account for thermodynamic properties. Contrary to expectations, carbonyl polarization or partial charges apparently are not an adequate explanation for fluoroketone electrophilicity.

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